IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

VERIFICATION OF TRANSLATION

I, Michael Wallace Richard Turner, Bachelor of Arts, Chartered Patent Attorney, European Patent Attorney, of 1 Horsefair Mews, Romsey, Hampshire SO51 8JG, England, do hereby declare that I am conversant with the English and German languages and that I am a competent translator thereof;

I verify that the attached English translation is a true and correct translation made by me of the attached specification in the German language of International Application PCT/EP2003/012532;

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _May 9, 2005_   _____

M W R Turner

BIOTRONIK GmbH & Co KG

Woermannkehre 1, 12359 Berlin

Use of one or more of the elements from the group yttrium, neodymium
and zirconium, and pharmaceutical compositions which contain those
elements

The invention concerns the medical use of one or more of the
elements from the group consisting of yttrium, neodymium and zirconium,
pharmaceutical formulations which contain those elements and implants
which are at least region-wise made up of such formulations.

Inflammation is used to denote the reaction of the organism, borne
by the connective tissue and the blood vessels, to an external or internally
triggered inflammation stimulus with the aim of eliminating or inactivating
same and repairing the stimulus-induced tissue damage. A triggering action
is effected by mechanical stimuli (foreign bodies, pressure, injury) and
other physical factors (ionising rays, UV-light, heat, cold), chemical
substances (lyes, acids, heavy metals, bacterial toxins, allergens and
immune complexes) as well as pathogens (micro-organisms, worms,
insects) or diseased metabolic products (out-of-control enzymes, malignant
tumors). The microbiological processes which are complex due to the
specified triggering factors generally involve the liberation of so-called
growth factors such as FGF, PDGF and EGF which stimulate proliferation,
that is to say the increase in tissue due to rampant growth or reproduction.

It will be noted that under certain medical indications proliferation
should be at least temporarily inhibited. In order to oppose the
reproductive activity of the cells or organisms, it is known for example to
use mitosis poisons, ionising rays or interferons for anti-viral action.

Particular requirements are involved in the treatment of coronary heart diseases. Coronary heart diseases, in particular acute myocardial infarctions, represent one of the most frequent causes of death in Western Europe and North America. In more than 80% of cases the cause of the myocardial infarction is thrombotic closure of a coronary artery due to rupture of an atheromatous plaque with pre-existing stenosing atheromatosis. Decisive factors for the long-term prognosis after acute myocardial infarction are as follows:

- effective and long-lasting re-dilation of the infarct artery,

- the duration of the thrombotic vessel closure,

- the prevention of greater myocardial loss and ventricular remodeling, and

- the mastery of rhythmogenic complications.

The specified factors determine not only cardiovascular mortality but also the quality of life after the infarction.

Non-operative methods of stenosis treatment have been established for more than 20 years, in which inter alia the constricted or closed blood vessel is dilated again by balloon dilation (PTCA – percutaneous transluminal coronary angioplasty). That procedure has proven its worth in particular in terms of therapy for acute myocardial infarction. It will be noted however that, with dilation of the blood vessel, very minor injuries, fissures and dissections occur in the vessel wall, which admittedly frequently heal up without any problem but which in about a third of the cases result in proliferation due to triggered cell growth, which ultimately result in renewed vessel constriction (restenosis). Dilation also does not eliminate the causes of the stenosis, that is to say the molecular-pathological changes in the wall of the vessel. A further cause of restenosis is the elasticity of the expanded blood vessel. After removal of the balloon the blood vessel constricts excessively so that the vessel cross-section is reduced (obstruction, referred to as negative remodeling). The latter effect can only be avoided by the placement of a stent.

In terms of interventional therapy for stable and unstable angina pectoris in the case of coronary heart disease, the insertion of stents has

2

resulted in a marked reduction in the rate of restenosis situations and thus better long-term results. That applies both in regard to primary stenosis and also recidivist stenosis. The higher level of primary lumen gain is the cause for using stent implantation.

5 An optimum vessel cross-section can admittedly be achieved by the use of stents, but it will be noted that the use of stents also results in very minor injuries which can induce proliferation and which thus can ultimately trigger restenosis. In addition the presence of such a foreign body initiates a cascade of cellular molecular processes which can result in progressive
10 blockage of the stent.

In the meantime extensive knowledge has been acquired relating to the cell-biological mechanism involved and the triggering factors in stenosis and restenosis. As already explained, restenosis occurs as a reaction on the part of the vessel wall to the local injury as a consequence of expansion of
15 the atherosclerotic plaque. By way of complex operative mechanisms, lumen-directed migration and proliferation of the smooth muscle cells of the media and the adventitia is induced (neointimal hyperplasia). Under the influence of various growth factors, the smooth muscle cells produce a cover layer of neointimal smooth muscle cells and matrix proteins (elastin,
20 collagen and proteoglycans) whose uncontrolled growth can gradually result in constriction of the lumen. Systemic drug therapy uses provide inter alia the oral administration of calcium antagonists, ACE inhibitors, anticoagulants, antiaggregants, fish oils, antiproliferative substances, antiinflammatory substances and serotonin antagonists, but hitherto
25 significant reductions in the kinds of restenosis have not been achieved in that way. A possible explanation for the disappointing results of all previous attempts of systemic application of the most widely varying substances is that systemic application cannot take the substance in an adequate level of concentration to the location of the vessel injury.

30 For some years now attempts have been made to reduce the risk of restenosis upon the implantation of stents by applying special coating systems. In part the coating systems serve as carriers, in which one or more pharmacologically effective substances are embedded (local drug

3

delivery or LDD). Local application makes it possible to achieve a higher tissue level, in which case systemic substance discharge remains low and thus systemic toxicity is reduced. The coating systems generally cover at least one peripheral wall of the endovascular implant, which is towards the vessel wall. Hitherto numerous preparations have been proposed as active substances or active substance combinations for LDD systems, for example Paclitaxel, Actinomycin, Sirolimus, Tacrolimus, Everolimus and Dexamethasone.

The carriers of coating systems of that kind comprise a biocompatible material which either is of natural origin or which can be produced synthetically. Particularly good compatibility and the possibility of influencing the elution characteristic of the embedded drug are afforded by biodegradable coating materials. Examples for the use of biodegradable polymers are cellulose, collagen, albumin, casein, polysaccharides (PSAC), polylactide (PLA), poly-L-lactide (PLLA), polyglycol (PGA), poly-D,L-lactide-co-glycolide (PDLLA/PGA), polyhydroxybutyric acid (PHB), polyhydroxyvaleric acid (PHV), polyalkylcarbonates, polyorthoesters, polyethyleneterephthalate (PET), polymalonic acid (PML), polyanhydrides, polyphosphazenes, polyamino acids and their copolymers as well as hyaluronic acid and its derivatives.

At the present time 80% of all stents are manufactured from medical steel (316L). In the course of time it has been found however that the material used is admittedly biocompatible but over medium and long periods of time it promoted in part thrombosis formation and in part adhesion of biomolecules to its surface. A further limitation in terms of biocompatibility of permanent stents is ongoing mechanical stimulus of the vessel wall. A starting point for resolving those problems is stents comprising a biodegradable material. The term biodegradation is used to denote hydrolytic, enzymatic and other metabolism-induced decomposition processes in the living organism, which result in a gradual dissolution of at least large parts of the implant. The term biocorrosion is frequently used synonymously. The notion of bioresorption additionally includes the subsequent resorption of the decomposition products. Thus for example a

4

large number of plastic materials have been proposed as the stent material, which admittedly exhibited good degradation behaviour but which by virtue of their mechanical properties are at most limitedly useful for medical application and – thus at least in the case of synthetic polymers based on PU and LDA derivatives – also cause a severe inflammatory reaction and stimulate neointima proliferation.

To overcome the above-indicated disadvantage, the use of special biodegradable metal alloys has recently been proposed, as are described in particular in DE 197 31 021 and DE 199 45 049. The metal alloys include special biodegradable iron, tungsten and magnesium alloys.

US No 6 264 595 discloses a stent which inter alia can contain radioactive yttrium isotopes, in which case the radiation produced upon disintegration of the isotopes is intended to prevent restenosis after stent implantation. US No 4 610 241 describes a method of treating atherosclerosis with ferro-, dia- or paramagnetic particles which, after placement at the location of the lesion, are heated up by alternating electromagnetic fields. The particles are to include inter alia given yttrium salts.

Zirconium is a constituent part of numerous ceramic biomaterials. Hitherto in vivo and in vitro investigations on special zirconium-bearing ceramics have not provided any pointers to a pharmacological effect in connection with smooth human muscle cells (Piconi, C, Maccauro G, (1999) *Biomaterials* 20, 1-25).

The object of the present invention is inter alia to provide agents for inhibiting the proliferation of human smooth muscle cells and pharmaceutical formulations, which are suitable in particular for use in endovascular implants such as stents.

In accordance with a first aspect of the invention that object is attained by the use of one or more of the elements from the group yttrium (Y), neodymium (Nd) or zirconium (Zr) for the production of a pharmaceutical formulation for inhibiting the proliferation of human smooth muscle cells.

5

It has now surprisingly been found that the proliferation of human smooth muscle cells, in particular arterial muscle cells, is markedly inhibited in the presence of yttrium neodymium and/or zirconium. In particular the use of those elements means that neointimal hyperplasia after balloon dilation can be reduced or even entirely prevented. The use of one or more of the elements from the group consisting of yttrium, neodymium or zirconium appears to be particularly suitable for the treatment of sclerotic, preferably atherosclerotic lesions. In the case of the pathophysiological processes which form the basis for restenosis, proliferation of smooth muscle cells which have previously migrated out of the media plays a crucial part. Inhibition of cell growth over a given period of time until the growth-stimulating factors are decomposed for the major part or completely can therefore effectively obviate restenosis. The elements yttrium, neodymium and/or zirconium are thus suitable in particular for restenosis prophylaxis after stent implantation. The reasons for the surprising pharmaceutical action of the elements yttrium, zirconium and/or neodymium on human arterial smooth muscle cells have not yet been completely clarified. Presumably the redox processes which take place in the cell medium with participation of the metals play an essential part.

Previous in vivo and in vitro investigations on mammals and fish in respect of the toxic and possibly pharmaceutical action of yttrium trichloride (YCl_3) have not provided any indications about the particular pharmaceutical action of yttrium on arterial human smooth muscle cells.

- With an intravenous administration of 1mg YCl_3/107g rat an increase in the aspartate and glutamate-pyruvate-transaminase activity was measured in the blood plasma 20 hours after administration, which points to liver damage (Hirano, S, Kodama, N, Shibata, K, and Suzuki, K T (1993) *Toxicol Appl Pharmacol* 121(2), 224-232).

- Intratracheally applied YCl_3 led to activation of the immune response in the lungs (Hirano, S, Kodama, N, Shibata, K, and Suzuki, K T (1993) *Toxicol Appl Pharmacol* 104(2), 301-311) and a rise in inflammatory markers (β-glucuronidase, lactate

6

dehydrogenase (LDH) and alkaline phosphatase) in the *bronchoalveolar lavage fluid* (BALF) (Suzuki, K T, Kobayashi, E, Ito, Y, Ozawa, H and Suzuki, E (1992) *Toxicology* (76(2), 141-152; Murubashi, K, Hirano, S, and Suzuki, K T (1998) *Toxicol Lett* 99(1), 45-51).

- A concentration of 15 µM YCl_3 in water leads to a reduction in the level of superoxide-dismutase activity in goldfish liver while catalase activity is only slightly impaired (Chen, Y, Cao, X D, Lu, Y and Wang, X R (2000) *Bull Environ Contam Toxicol* 65(3), 357-365).

- The 'isolated organ technique' demonstrated that YCl_3 reduces the amplitude of the peristaltic activity of rat intestine (Cunat, L, Membre, H, Marchal, L, Chaussidon, M and Burnel, D (1998) *Biol Trace Elem Res* 64(1-3), 43-59).

- In vitro a genotoxic action of YCl_3 on human lymphocytes was demonstrated (Yang, H, Ji, Q, and Zhang, X (1998) *Zonghua Yu Fang Yi Xue Za Zhi* 32(3), 156-158).

- YCl_3 blocks Ca^{2+} channels *in vitro* (Beedle, A M, Hamid, J, and Zamponi, G W (2002) *J Membr Biol* 187(3), 225-238; Minar, B, and Enyeart, J J (1993) *J Physiol* 469, 639-652).

There are also studies about the influence of yttrium on the proliferation of bacteria. Investigations were conducted into *Tetrahymena shanghaiensis* (Wang, Y, Zhang, M and Wang, X (2000) *Biol Trace Elem Res* 75(1-3), 265-275), *Klebsiella pneumoniae* strain 204 and K9 (Aleksakhina, N N, Miriasova, L V and Basnak'ian, I A (2002) *Zh Mikrobiol Epidemiol Immunobiol* (6), 13-18) and also *Pseudomonas fluorescens* (Appanna, V D, Hamel, R D, Pankar, E and Puiseux-Dao, S (2001) *Microbios* 106(4-13), 19-29). In that case there was found to be increased proliferation for *T. shanghaiensis* and *P. fluorescens* at low levels of yttrium concentration and an antiproliferative action at high levels of concentration. For *K. pneumoniae* a comparative high level of concentration (142mM $Y(OH)_3$) was tested, which resulted in increased proliferation.

A second aspect of the invention concerns pharmaceutical formulations containing one or more of the elements from the group yttrium, neodymium or zirconium.

An advantageous adaptation of the pharmaceutical formulation provides that the formulation includes an at least very substantially biodegradable carrier which is broken down in vivo with a predetermined degradation performance. The term 'degradation performance' is used to denote the breakdown of the carrier in the living organism, which takes place over time, due to chemical, thermal, oxidative, mechanical or biological processes. This aspect of the invention is of significance in particular when the formulation is to be suited for intravascular liberation after implantation in a vascular vessel. In particular local application of the active substances is to be effected in the region of the lesion to be treated. Such procedures can be summarised by the term 'local drug delivery' (LDD).

In accordance with a preferred variant the biodegradable carrier is an alloy, in particular a magnesium, iron or tungsten alloy. Metal alloys of that kind are known for example from DE 197 31 021 and DE 199 45 049. A further, particularly suitable formulation based on a magnesium alloy is of the following composition:

Magnesium: > 90%

Yttrium: 3.7% to 5.5%

Rare earths (without yttrium): 1.5% to 4.4%

Balance: < 1%.

Preferably the formulation further includes a magnesium alloy with a content of yttrium in the range of between 3.7 and 5.5% by weight, a content of neodymium in the range of between 1.8 and 2.7% by weight and a content of zirconium in the range of between 0.2 and 1.2% by weight. In a particularly preferable feature the formulation corresponds to the commercially available magnesium alloy WE43 (W-25 EP 5M). The above-mentioned materials and details relating to the composition are distinguished by their good workability and favourable liberation performance for yttrium, neodymium and zirconium upon in vivo

8

breakdown of the carrier. The literature includes inter alia a study relating to the degradation performance of a magnesium alloy under physiological conditions, which provides indications as to which factors and measures are to be observed when optimising active substance liberation (Levesque, J, Dube, D, Fiset, M and Mantovani, D (2003) *Material Science Forum Vols* 426-432 pp, 225-238).

In accordance with a further variant of the formulation according to the invention the carrier is a biodegradable polymer and one or more of the elements from the group yttrium, neodymium or zirconium is embedded in the form of powders or microparticles in the polymer. Due to the gradual breakdown of the polymer in vivo, the powder or the microparticles is or are slowly liberated and can deploy their pharmacological action after bioresorption. The polymer carrier can be in particular hyaluronic acid, poly-L-lactide or a derivative of the polymers.

It is further preferred if the formulation contains yttrium in a quantitative proportion of between 0.1 and 10% by weight, neodymium in a quantitative proportion of between 0.1 and 5% by weight and/or zirconium in a quantitative proportion of between 0.1 and 3% by weight, in each case with respect to the total weight of the formulation.

It is known from cell culture tests that the elements of the group yttrium, neodymium and zirconium, in certain ranges of concentration, exhibit an antiproliferative behaviour on arterial human smooth muscle cells. The formulation according to the invention, insofar as it includes yttrium, is therefore so adapted that an yttrium concentration in the region of the human smooth muscle cells to be treated is between 200 µM and 2 mM, in particular between 800 and 1 mM. If the composition contains neodymium, then the formulation is preferably so adapted that there is a neodymium concentration in the region of the human smooth muscle cells to be treated of between 600 µM and 2 mM, in particular between 800 µM and 1 mM. If zirconium is a constituent of the formulation, a zirconium concentration in the region of the human smooth muscle cells to be treated is preferably to be predetermined by targeted adaptation of the formulation at between 200 µM and 2 mM, in particular between 200 µM and 1 mM. In

9

the case of a formulation which contains yttrium, neodymium and zirconium, it is particularly preferable for the formulation to be so adapted that there is an yttrium concentration at between 350 and 550 µM, a neodymium concentration at between 100 and 200 µM and a zirconium concentration at between 10 and 30 µM in the region of the human smooth muscle cells to be treated. The specified concentration ranges appear to be particularly suitable for restenosis prophylaxis after stent implantation as the systemic substance discharge is very slight and therefore at most a low level of systemic toxicity has to be reckoned with.

The actual levels of concentration in the living organism are dependent on the degradation performance of the formulation, which in turn depends on the specific composition of the formulation and the diffusion performance of the decomposition products in the tissue. Theoretical predictions can only be made with difficulty here and suitable measurements frequently suffer from major measurement errors. So that the above-indicated concentration ranges occur in the environment of the human smooth muscle cells to be treated, experimental studies relating to bioresorption of the selected formulation are therefore generally also necessary.

The applicants' own experiments demonstrate inter alia a statistically significant reduction in neointima formation in pigs when using the alloy WE43 and the resulting degradation performance (substantial biodegradation within 2 months). The coronary stents used there were of a weight of 3 mg and contained 123 µg of yttrium (4.1% by weight), 66 µg of neodymium (2.2% by weight) and 15 µg of zirconium (0.5% by weight).

A third aspect of the invention concerns implants which have an at least region-wise coating consisting of the above-mentioned formulation according to the invention or which in parts structurally comprise said formulation. Such an implant can preferably be in the form of an endovascular support device (stent).

Distribution and mass of the formulation in a stent is preferably predetermined with respect to the length of the stent in such a way that there is between about 5 and 30 µg/mm, in particular between 10 and 20

10

µg/mm, of yttrium. For neodymium that is preferably fixed at between about 2 and 20 µg/mm, in particular between 3 and 10 µg/mm, while for zirconium it is preferably at between about 0.05 and 10 µg/mm, in particular between 0.5 and 6 µg/mm. The stated limits of the ranges permit

5   pharmacodynamically favourable local application of the active substances.

A fourth aspect of the invention concerns the already known elements or combinations of elements from the group of yttrium, neodymium or zirconium, with which no therapeutic action was yet associated, as therapeutic agents. In particular this aspect concerns alloys

10   which contain one or more elements from the group yttrium, neodymium or zirconium. According to the applicants' own knowledge hitherto a therapeutic action was not associated with any of the elements/alloys. Indications in regard to the antiproliferative action of one or more of the elements from the group yttrium, neodymium and zirconium, their alloys or

15   their use in pharmaceutical formulations are not to be found in the state of the art.

The invention is described in greater detail hereinafter by means of embodiments and with reference to accompanying drawings in which:

Figure 1 shows a Table to illustrate the dependency of the vitality of

20   arterial human smooth muscle cells on the concentration of yttrium, neodymium or zirconium after three days,

Figure 2 shows a further Table to illustrate the dependency of the proliferation of smooth human muscle cells on the concentration of yttrium, neodymium or zirconium after three days,

25   Figure 3 shows a diagrammatic view of an endoprosthesis in the form of a stent,

Figure 4 shows a typical section through a main coronary vessel of a pig after implantation of a conventional stent, and

Figure 5 shows a typical section through a main coronary vessel of a

30   pig after implantation of a stent comprising the material WE43.

<u>Testing of yttrium chloride (YCl₃), zirconium chloride (ZrCl₄) and neodymium chloride (NdCl₃) in cell culture</u>

11

The Tables of Figures 1 and 2 are based on test series on arterial human smooth muscle cells with a concentration in the range of between 1 mM and 1 μM, for yttrium, neodymium and zirconium respectively. The tests were carried out as follows:

5   The action of $YCl_3 \times 6H_2O$, $ZrCl_4$ and $NdCl_3$ on the vitality and proliferation of human arterial smooth muscle cells (SMC) was investigated. It is to be assumed that the elements are oxidised in a physiological environment and bioresorption of the rare earth ions Y^{3+}, Zr^{4+} and Nd^{3+} takes place. The tests were conducted in concentration ranges of between 1 mM and 1 μM, in each case with respect to the content of rare earths. Lower levels of concentration exhibited no effects.

The substances were dissolved in water or ethanol ($ZrCl_4$) respectively (strain solution 0.1 M, in each case in relation to the concentration of rare earths). Upon dilution in cell culture medium, at higher levels of concentration, deposits are formed, which could be reduced by ultrasonic treatment but not completely eliminated. The eluates produced were incubated with primary cell cultures of human arterial smooth muscle cells (SMC) (3 days, 37°C). The cell vitality (MTS test) and cell proliferation (BrdU test) were investigated. For that purpose tests were performed similarly to a cytotoxicity testing procedure in accordance with DIN EN 30993-5. The results of those tests are summarised in Table 1 (vitality) and Table 2 (proliferation).

The vitality of arterial human smooth muscle cells rose in the concentration range of between 1 μm and 100 μm. Levels of concentration of >800 μM of neodymium and zirconium resulted in a drop in vitality.

The proliferation of arterial human smooth muscle cells was increasingly greatly inhibited with levels of neodymium concentration ≥800 μM. Proliferation inhibition which was already extensive was to be found with levels of yttrium concentration of ≥800 μM. With levels of zirconium concentration of between 200 μM and 1 mM the proliferation was on average 44%. Accordingly yttrium and neodymium at higher levels of concentration exhibited a great action on the proliferation of smooth muscle cells. Zirconium had a moderate antiproliferative action.

12

<u>Testing of WE43 eluates in a cell culture</u>

Sterilised sample bodies of the alloy WE43 weighing about 1 mg were eluted with 2 ml cell culture medium at 37°C in a cell culture cabinet for 13 days, in which case the sample body is only incompletely dissolved.

5 Primary cell cultures of human arterial smooth muscle cells (SMC) were then incubated with 1 ml of the eluate and 1 ml of fresh cell culture medium (4 days, 37°C). Cell activity (MTS test) and cell proliferation (BrdU test) were investigated. For that purpose tests were performed similarly to a cytotoxicity testing procedure in accordance with DIN EN 30993-5.

10 The proliferation of smooth muscle cells was 91% inhibited upon incubation with eluates of the alloy WE43 in comparison with control cells (SMC + medium). The cell activity of the smooth muscle cells for the alloy WE43 was 95%.

<u>Animal tests on pig</u>

15 Figure 3 shows a vascular endoprosthesis in the form of a tubular stent 10 whose basic structure is composed of a plurality of individual legs 12. The basic structure of the stent 10 can be divided in the longitudinal direction into individual support portions 14 which are each composed of legs 12 folded in a zig-zag or meander configuration and which extend in

20 the peripheral direction. The basic structure of the stent 10 is formed by a plurality of such support portions 14 which occur in succession in the longitudinal direction. The support portions 14 are connected together by way of connecting legs 16. Each two connecting legs 16 which are mutually adjacent in the peripheral direction and the sub-portions of the support

25 portions 14, which are disposed in mutually opposite relationship between those connecting legs 16, define a mesh 18 of the stent 10. Such a mesh 18 is shown emphasised in Figure 1. Each mesh 18 surrounds a radial opening of the peripheral wall or the basic structure of the stent 10.

Each support portion 14 has for example between three and six

30 connecting legs 16 which are equally distributed over the periphery of the stent 10 and which respectively connect a support portion 14 to the adjacent support portion 14. Accordingly the stent 10 has between three

and six meshes in each case in the peripheral direction between two support portions 14.

By virtue of the folding of the legs 12, the stent 10 is expandable in the peripheral direction. That is effected for example with a per se known balloon catheter (not shown here) which at its distal end has a balloon which is expandable by means of a fluid. The stent 10 is crimped in the compressed condition on to the deflated balloon. Upon expansion of the balloon, both the balloon and also the stent 10 are enlarged. The balloon can then be deflated again and the stent 10 comes loose from the balloon. In that way the catheter can serve simultaneously for insertion of the stent 10 into a blood vessel and in particular into a constricted coronary vessel and also for expansion of the stent at that location.

The basic structure of the stent 10 shown in Figure 3 comprises the biodegradable magnesium alloy WE43 of the following formulation:

Zirconium: 0.53% by weight

Yttrium: 4.1 % by weight

Neodymium: 2.2 % by weight

Others: <0.4% by weight

Magnesium: balance to 100% by weight.

If a weight of 3 mg is assumed for a 10 mm long stent of WE43, it contains about 123 μg/1.384 μM yttrium (4.1% by weight), about 66 μg /458 μM neodymium (2.2% by weight) and about 15 μg/164 μM zirconium (0.5% by weight). Per mm of stent length, there is a maximum liberation of 12.3 μg/138.4 μM yttrium, 6.6 μg/45.8 μM neodymium and 1.5 μg/16.4 μM zirconium.

In animal tests on pigs, stents of the above-mentioned magnesium alloy were compared with conventional silicon carbide-coated stents by means of coronary angiography and morphometric evaluation of histological section preparations. For that purpose conventional stents of medical high-grade steel with a passive silicon carbide coating and stents of WE43 were implanted in all three coronaries of pigs. A quantitative control angiography (QCA) was effected in each case after four and eight weeks, in which case breakdown in the case of the biodegradable stent in the pig was very

14

substantially concluded after about 8 weeks. In addition cardiac preparations of the animals were produced after 8 weeks for histological processing.

The results of the coronary angiography and histological section preparations demonstrate a marked trend towards a reduction in surface stenosis when using WE43. The histology exhibited a substantially uniform image in relation to neointima formation after eight weeks. In that respect the magnesium implants were found to be less proliferative than the control implants. Thus an average neointima surface formation of 1.23 mm^2 was found when using WE43, in comparison with 2.9 mm^2 in the case of a conventional implant.

Figure 4 shows a typical section through a coronary vessel of a pig upon implantation of a conventional stent with silicon carbide coating after eight weeks while Figure 5 shows a corresponding histological section for a WE43-based implant. It will be clear that neointima formation which can be estimated by the morphometric cross-section of the neointima surfaces after eight weeks is reduced approximately by a factor of 2 when using WE43. The effect appears to be caused essentially by the residues which are liberated upon degradation of the stent into the surrounding tissue and which in turn contain yttrium, neodymium and zirconium.